Remarks

Applicant has carefully studied the final Office Action, mailed May 27, 2010 (hereinafter "the Action"). Applicant believes these explanatory remarks are fully responsive to the Action. Accordingly, this important patent application is now in condition for allowance.

Status of the Claims

Claims 19, 23, 26, and 27 were pending and under consideration. Claim 23 has been amended. Support for the amendment can be found in the original specification and figures. No claims have been added or canceled. Therefore claims 19, 23, 26 and 27 are presented for consideration.

Claim Rejections - 35 U.S.C. §103(a)

Claims 19, 23, 26 and 27 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Thiesing et al. (Blood, 2002) (hereinafter "Thiesing") over Virginia Commonwealth University (WO 02/22133 A1) (hereinafter "VCU"). Applicant respectfully traverses these rejections on the basis that the cited combination produces unexpected results; there is no motivation to combine the references; and the cited combination fails to teach each and every limitation of the claims.

Claim 19

Claim 19 discloses a method for inducing apoptosis in imatinib mesylate refractory cancer cells, comprising contacting the living cells with a imatinib mesylate and suberoylanilide hydroxamic acid wherein the living cells are selected from the group consisting of chronic myelogenous leukemia cells and acute lymphoblastic leukemia cells.

Unexpected Results

MPEP §2143.02 states that in order to support a claim of obviousness all claim elements must be known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded no more than predictable results to one of ordinary skill in the art.

An express limitation of claim 19 is the administration of imatinib mesylate and suberoylanilide hydromaxic acid (SAHA). The Office acknowledges on page 4 that Theising does not teach supplementing STI571 (imatinib mesylate) with suberoylanilide hydromaxic acid (SAHA) and that VCU does not teach the combination of SAHA with imatinib mesylate. However, the Office reasons that since both VCU and Theising teach that each agent may be supplemented with another agent known to treat leukemia, the references can be combined to obviate the present invention. Applicant asserts that the combination would not have yielded predictable results.

Applicant respectfully submits that not every agent used to treat leukemia can be combined with every other agent that is used to treat leukemia as is proposed by the Office. The state of the art at the time of the invention was that it was not known if cancer therapeutics could be combined to enhance their effects. Theising illustrates the uncertainty at the time of invention by stating on page 3198 that the possibility of antagonism between STI571 and antileukemic agents was a major reason for undertaking the studies. Theising provides direct evidence that some agents used to treat leukemia, when combined with STI571, exhibit an antagonistic effect.

Theising examined the inhibition of cell proliferation by combining STI571 with four different antileukemic agents used in the treatment of CML: hydroxyurea (HU), interferon-alpha (IFN), daunorubicin (DNR), and cytosine arabinoside (Ara-C). (Abstract) Applicant respectfully notes that none of the agents tested was a histone deacetylase inhibitor such as SAHA. HU is believed to operate via the reduction of the production of deoxyribonucleotides through its inhibition of ribonucleotide reductase. IFN is a cytokine that is used as an immunotherapeutic to mobilize the immune system and interfere with the ability of the cancer cells to proliferate. DNR is a chemotherapeutic of the anthracyline family that binds to DNA and distorts the helical formation. Ara-C is an anti-metabolic agent that rapidly converts into cytosine arabinoside triphosphate which damages DNA when the cell cycle holds in S phase. The administration of each of the agents in combination with STI571 produced differing effects. Theising found that

out of four agents tested: two agents (IFN and DNR) exhibited an additive effect when combined with STI571; one agent (Ara-C) exhibited a synergistic effect when combined with STI571; and **one agent (HU) exhibited an antagonistic effect** when administered with STI571.

The Office states on page 7 that since both Theising and VCU teach that apoptosis occurs when each of the agents is contacted with the cells and that each reference teaches the combination with another agent known to treat leukemia, the instant invention is obviated. The Office further states on page 8 that each element could be combined and would have performed the same function as it did separately and the results would have been predictable. As stated *supra*, Theising fails to teach supplementing STI571 with suberoylanilide hydroxamic acid and the Office offers VCU to overcome this deficiency. VCU discloses the co-administration of **cyclin-dependent kinase inhibitors** with cellular differentiation agents, such as SAHA, to promote apoptosis in cancer cells. Applicant respectfully notes that imatinib mesylate is **not** a cyclin-dependent kinase inhibitor nor is it a cell differenatiation agent. Applicant respectfully asserts that the results shown in Theising, particularly with regard to the administration of HU and STI571, illustrate that not all chemotherapeutic agents can be combined to produce enhanced effectiveness. Each of the agents used in Theising were also used successfully on their own to treat cancer cells to reduce cell proliferation, however the combination of HU with STI571 produced an **antagonistic effect**. The fact that one chemotherapeutic agent, known to be effective in the treatment of cancer, when combined with another chemotherapeutic agent (also known to be effective in the treatment of cancer) produced **antagonistic results**, provides strong evidence that the results of the combination of two different chemotherapeutic agents are not predictable.

As established *supra*, the state of the art at the time of the invention was that it was not known if different chemotherapeutic agents could be combined without producing an antagonistic result. Prior to Applicant's administration of SAHA and imatinib mesylate together, it was not known the drugs had a synergistic or additive effect hence there was no reason to combine them.

Applicant also respectfully asserts that differences in the types of cells that are administered the various chemotherapeutic agents between the two references also contributes to the uncertainty as to the results of the cited combination. Theising found that differing cell types had differing

responses to the administration of STI517 and various other agents for treating leukemia. The cells examined in VCU were not imatinib mesylate refractory cells nor were they CML or ALL cells. Furthermore, the cells used in VCU differed from the cells used in Theising. One would not have a reasonable expectation of success in combining imatinib mesylate as done in Theising with SAHA as disclosed in VCU.

Applicant respectfully asserts that due to the differences in the underlying mechanisms of the agents, the differing cell types administered to, and the differing results obtained by Theising indicating that combining different chemotherapeutic agents with imatinib mesylate gave a range of results from synergistic to antagonistic, one of ordinary skill in the art would not achieve predictable results.

No Motivation to Combine

As established previously, Theising discloses the use of STI571 in the treatment of leukemia but does not teach supplementing STI571 with suberoylanilide hydroxamic acid (SAHA). The Office uses VCU to overcome this deficiency. VCU teaches the administration of **cyclin dependent kinase inhibitors** with cellular differentiation agents to promote apoptosis in cancer cells. VCU discloses that SAHA is one type of cellular differentiation agent that can be used. Claim 19 expressly discloses the administration of imatinib mesylate and SAHA. Applicant respectfully reasserts that imatinib mesylate is a **tyrosine kinase inhibitor** which by itself causes apoptosis. Tyrosine kinase inhibitors inhibit the action of protein kinases particularly the phophorylation of tyrosine. Particularly, imatinib mesylate binds to Bcr-Abl receptors blocking ATP. The underlying mechanism of tyrosine kinase inhibitors differs from the mechanisms of the cyclin dependent kinase inhibitors disclosed in VCU. The **cyclin-dependent kinase inhibitors** disclosed in VCU oppose apoptosis. (page 3, lines 16-17) Cyclin-dependent kinase inhibitors block cell cycle progression. (page 4, lines 5-8)

The Office states on page 8 that VCU teaches that one agent alone (FP alone) had a minimal effect on apoptosis and that the co-administration of a cyclin-dependent kinase and a cellular differentiation agent (PMA and FP) resulted in a synergistic drug interaction. The Office further states that VCU teaches that its method involves co-administering to the cancer cells a cyclin dependent kinase inhibitor and an agent that induces cellular differentiation, such as SAHA.

Applicant is not denying that SAHA is a cellular differentiation agent. Similarly Applicant is not disputing that VCU found that the co-administration of PMA (a cell differentiation agent) with FP (a cyclin dependent kinase inhibitor) resulted in synergistic results. Applicant is asserting that there is no motivation to combine the references since VCU expressly teaches, as the Office has acknowledged, the co-administration of a cyclin dependent kinase inhibitor and a cellular differentiation agent and **imatinib mesylate is neither a cellular differentiation agent nor a cyclin dependent kinase inhibitor.** As stated *supra*, imatinib mesylate is a tyrosine kinase inhibitor that functions in an entirely different manner than the cyclin dependent kinase inhibitors disclosed in VCU. Given the difference in underlying mechanisms between the cyclin-dependent kinase inhibitors and the tyrosine kinase inhibitors, there is no motivation to combine the references and it cannot be said that the concurrent administration of imatinib mesylate with SAHA would yield predictable results.

Claim 23

Claim 23 depends from claim 19 and further recites the limitation that the cells are **continuously exposed to** the imatinib mesylate and the suberoylanilide hydroxamic acid for about 48 hours. The Office states on page 9 that the instant specification teaches that the process of "contacting" the target cells is accomplished by "administering" a tyrosine kinase inhibitor and a histone deacetylase inhibitor to the subject. Applicant respectfully asserts that paragraph [0024] of the instant specification states that combined treatment with SAHA and imatinib mesylate for 48 hours induced more apoptosis of target cells as compared to the treatment with either agent alone. Further, "[e]ffectiveness of the combination of the agents was effective on an **exposure-dependent**, shorter exposures to the combination induced a lesser apoptotic effect." (emphasis added) The Office states on page 9 that VCU teaches the administration of a histone deacetylase inhibitor with another agent known to treat leukemia and teach co-administration within the time range of 24-72 hours which overlaps and encompasses the claimed 48 hours. Applicant respectfully asserts that the co-administration of the agents disclosed in VCU refers to the time window of **when the agents can be added**, not continuous contact with the cells. As such, the cited combination fails to teach each and every limitation of the claims and cannot be said to obviate.

Claim 26 and 27

Claim 26 depends from claim 19 and further recites the limitation that the cancer cells are chronic myelogenous leukemia cells that are either accelerated-phase or blast crisis phase. Claim 27 recites the limitation that the cancer cells are acute lymphoblastic leukemia cells that are either accelerated-phase or blast crisis phase. The Office states on pages 9-10 that Theising teach that resistance would develop with long term administration of STI571 and suggest the combination of STI571 with other agents to prevent the emergence of resistant clones or to enhance the eradication of the leukemic clone. Applicant respectfully reasserts that the combination of Theising and VCU fails to teach inducing apoptosis in CML or ALL accelerated-phase or blast-phase cells. Theising expressly states on page 3199 that the **results of the study are applicable to chronic phase patients whose current treatment regimens include low-dose, continuous exposure to agents such as IFN and Ara-C**. Theising goes on to state that in acute leukemia patients, anti-leukemic agents are typically given as high-dose bolus infusion. High dose bolus infusions are the exact opposite of the low-dose continuous exposure patients that Theising expressly states the results of the study are applicable to. The cancers treated in VCU do not include accelerated or blast crisis CML cells. Neither of the references, nor their combination, teach the administration of either drug to chronic myelogenous leukemia cells or acute lymphoblastic leukemia cells in accelerated or blast crisis phase. Given that the cited combination of references fails to teach each and every limitation of the claims, the cited combination cannot be said to obviate.

Conclusion

For the foregoing reasons it is submitted that the Office cannot maintain a *prima facie* case of obviousness as required under 35 U.S.C. § 103(a). It is therefore respectfully requested that the rejection of claims 19, 23, 26 and 27 under 35 U.S.C. § 103(a) be withdrawn.

Conclusion

Entry of a Notice of Allowance is solicited. If the Office is not fully persuaded as to the merits of Applicant's position, or if an Examiner's Amendment would place the pending claims in condition for allowance, a telephone call to the undersigned at (813) 925-8505 is requested.

Very respectfully,

SMITH & HOPEN

/michele l lawson/

By:_____

Dated: July 8, 2010

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CERTIFICATE OF ELECTRONIC TRANSMISSION

(37 C.F.R. 2.190 (b))

I HEREBY CERTIFY that this correspondence is being electronically transmitted to the Patent and Trademark Office through EFS Web on July 8, 2010.

/lauren reeves/

Date: July 8, 2010

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Lauren Reeves